Health & Safety Report

Worker Health and Safety Branch

HS-1673

ILLNESSES ASSOCIATED WITH EXPOSURE TO ALDICARB IN CALIFORNIA, 1982 - 1990

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December 13, 1994

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Executive Summary

Background

We reviewed cases associated with aldicarb reported to the California Pesticide Illness Surveillance Program (PISP) between 1982 and 1990 as a response to concerns that this compound accounted for excessive number of illnesses in proportion to the amount of aldicarb used. The carbamate insecticide aldicarb (Temik®) is an N-methylcarbamate cholinesterase (ChE) (a nervous system enzyme in a broad range of insects, birds, mammals and other animals) inhibiting insecticide, first introduced in the 1960's for systemic control of a variety of insects, mites, and nematodes. The principal uses in California have included preplant treatment on cotton (79% of all pounds of aldicarb used), sugarbeets, ornamental flowers, and potatoes. The principal safety concern with aldicarb is its extreme acute toxicity. Its oral LD50 (a benchmark for systemic toxicity, the dose required to kill half of a test animal population) for this compound is between 0.46 and 1.23 mg/kg body weight in the rat. The dermal LD50 (akin to the oral LD50, but measured following application of aldicarb to the skin) ranges between 3.2 and slightly more than 10 mg/kg in the rat. Despite its high toxicity, reported illnesses linked to the use of this product have been principally associated with its accidental or deliberate misuse.

Methods

We reviewed cases identifying aldicarb as one of the possibly related exposures reported to PISP between 1982 and 1990. The methodology was similar to that used in previous reviews of other cholinesterase inhibitors. Case review involved manual scrutiny of PISP files for all cases identified from the computer source files. Information extracted included symptoms present, exposure history, and cholinesterase data, where present. Aldicarb associated cases involving suspected systemic illness were then compared with a large data base on suspected systemic illnesses associated other cholinesterase inhibiting compounds in California during the same 1982-1990 time period. As part of a separate project these cases were manually reviewed in an identical manner. Comparisons were made based on the relative frequency of definite (ChE depression accompanied by one or more compatible symptoms) and probable (defined by the presence of specific symptoms) ChE-related illness in the two sets of exposure. Systematically evaluated exposure variables included specific ChE inhibitors, application work, exposure to field residue, and pesticide drift. The difference in frequency of ChE- related illness between the two sets of cases was measured by calculating an epidemiologic measure known as the Odds Ratio (OR).

Results

Between 1982 and 1990, the PISP source file contained records for 93 cases of illness associated with suspected exposure to aldicarb, with 89 (95.7%) records containing sufficient information to classify the relationship between exposure and illness. Of the cases with sufficient information to classify, 78 (87.6%) involved suspected systemic illness. In 48 of these cases (61.5%), aldicarb was the only ChE inhibitor involved. In 30 (38.5%) the reported exposure involved at least one organophosphate compound (another large class of cholinesterase inhibiting insecticides that produces symptoms identical to those produced by aldicarb poisoning). In a selected set of cases that met criteria for a case-comparison study, the overall frequency of ChE-related illness for exposures to aldicarb did not differ significantly from exposures to other ChE inhibitors ($OR = 1.67$, $p = 0.47$ by Yates P^2).

By exposure category, application associated exposures had a non-significant increased frequency of ChE-related illness compared to cases in the remaining exposure categories ($OR = 2.63$, $p = 0.124$ by Fisher's two-tailed exact test [FET]). None of the field residue exposures involved ChE-related illness. However, this reduction in the frequency of ChE-related illness was based only on six cases and was not statistically significant from the remaining aldicarb exposure categories (OR = undefined, $p = 0.58$, by FET). Only one subject with aldicarb field residue exposure met criteria for inclusion in the case-control file and did not have ChE-related illness. As expected, comparison with other ChE inhibitors produced an undefined odds

ratio and showed that the reduction of frequency of illness for aldicarb associated field residue exposures was not statistically significant when compared to other ChE inhibitors.

Of the 12 subjects with aldicarb ingestion exposures, six (50.0%) exhibited ChE-related illness. This is a frequency significantly higher than subjects in the remaining exposure categories ($OR = 8.43$, $p = 0.0036$). The most serious case reported involved a near fatal childhood poisoning of a 2-year old girl who resided in a trailer at the edge of a field being planted with aldicarb treated cotton seed (630-90). Details of this case are available in a prior DPR report. Eleven cases resulted from possible ingestion of aldicarb residues in illegally treated produce, but included only two cases (1460-85 and 1609-85) resulting from a large cluster estimated to involve several hundred individuals who ingested contaminated watermelon in 1985. Four cases resulted from illegal application of aldicarb to squash grown in a home garden (893-83 and related cases), a single case from a similar application of aldicarb to a garden fruit tree (1583-83), and four cases involved a family that ingested parts of watermelon intended for seed production that contained 0.3 ppm of aldicarb.

Conclusion

Compared to other exposure categories, the highest frequency of ChE-related illness was associated with accidental ingestion of aldicarb residues. This category accounted for nearly half of the ChE-related illness, including a near-fatal childhood poisoning. All but three of the cases of cholinesterase depression in this series appear to have been caused by misuse of aldicarb. Three applicators who became ill claimed to have complied with all safety procedures, but there is no independent confirmation of their compliance. Because violations of proper application procedure are routinely accompanied by civil penalties, it is possible that some violations of application procedure may not have been disclosed. The overall frequency of ChE-illness in the routine application category was not elevated compared to other ChE inhibitors.

Introduction

We reviewed cases associated with aldicarb reported to the California Pesticide Illness Surveillance Program (PISP) between 1982 and 1990 as a response to concerns that this compound accounted for excessive number of illnesses in proportion to the amount of aldicarb used.[a] In this study, we approach the comparative hazard presented by aldicarb by evaluating the relative frequency of definite and probable illness among cases associated with exposure to aldicarb and those associated with other cholinesterase inhibitors.

Background

Uses and physical properties

The carbamate insecticide aldicarb (Temik®) is an N-methylcarbamate cholinesterase inhibiting insecticide, first introduced in the 1960's for systemic control of a variety of insects, mites, and nematodes. The principal uses in California have included granular aldicarb on cotton (79% of all pounds of aldicarb used), sugarbeets, ornamental flowers, and potatoes.[1] In 1986, granular aldicarb was reformulated to reduce the level of dust associated with its application.[2]

Notable physical properties include a vapor pressure of $1x10^{-4}$ mm Hg at 25EC, limited solubility in water, and marked solubility in common organic solvents. Decomposition takes place readily in alkaline conditions at temperatures above 100EC.[3]

Acute toxicity

Animal tests indicate that aldicarb does not cause dermal irritation or sensitization or other important non-systemic effects.[4] However, the systemic toxicity of aldicarb, secondary to acute inhibition of acetylcholinesterase, is extreme. The oral LD50 for this compound is between 0.46 and 1.23 mg/kg in the rat and the dermal LD50 ranges between 3.2 and > 10 mg/kg in the rat. Despite its high toxicity, reported illnesses linked to the use of this product have been principally associated with its accidental or deliberate misuse.[5]

Methods

We reviewed cases identifying aldicarb as one of the possibly related exposures reported to PISP between 1982 and 1990. The methodology was similar to that used in previous reviews of other cholinesterase inhibitors.[6 7]

Cases were extracted from the PISP source file for each year between 1982 and 1990 based upon identification of aldicarb in one of the pesticide identification fields. Cases originally classified as unrelated to pesticide exposure were also reviewed in order to identify individuals who were part of illness clusters involving suspected exposure to aldicarb. The review focused on systemic illness, but included reports of skin or eye injury, and exposed, asymptomatic individuals who sought medical evaluation in cluster illness episodes. No differentiation was made between cases identifying aldicarb as the primary pesticide from those identifying it as a secondary exposure. Case review involved manual scrutiny of PISP files, including pesticide episode investigation reports (PEIRs) filed by the county agricultural commissioners, doctor's first reports of occupational illness or injury (DFRs), pesticide illness reports (PIRs) and priority investigation reports for all cases identified from the computer source files. Information extracted included symptoms present, exposure history, and cholinesterase data, where present.

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[a] unpublished analysis, U.S. E.P.A., Office of Pesticide Programs

Coding of Demographic Information

In addition to information specifically related to work exposure and illness, we coded demographic variables not originally coded in the original PISP file. These included sex, age, and ethnicity (based on Hispanic vs. non-Hispanic surname). Standard industrial classification (SIC) codes[8 9 10] were used to identify categories of employment [major industrial divisions, and major subdivisions of agriculture].

Statistical methods and Selection of Case and Comparison Subjects

The case group was selected from the entire OP case file based on the occurrence of definite and probable illness and employment in an agricultural SIC code. For descriptive purposes, this group was termed the ChE illness group. The comparison, or control, group included all subjects from the OP case file employed in agriculture and classified as unlikely illness, or unrelated illness, asymptomatic without evidence of ChE depression. Also included in the comparison group, were symptoms compatible with ChE effect but with reported ChE activity within the normal population range, as reported by the testing lab. For descriptive purposes, this group was termed the non-ChE effect group.

The SPSS/PC statistical analysis program[11] was used for analyzing the coded information by exposure and illness category. Possible biases in reporting by demographic categories were evaluated by comparing summary demographic information with previously published information about the California agricultural workforce.[12 13 14 15 16 17 18] The distribution of SIC categories represented by the study subjects was also evaluated to determine the percent of the total agricultural population represented compared to the SIC categories not represented among the study subjects. Reported annual average employment for each agricultural SIC code was derived from data gathered from state unemployment insurance tax records and data for each year between 1982 and 1990 published by the U.S. Bureau of Labor Statistics.[19]

The odds (odds ratio [OR])[20] of developing definite or probable illness following OP exposure was calculated for potential risk factors including pesticide application work, field work, drift exposure, and individual OP compounds that accounted for 10 or more reported exposures. A Yates' chi-square was used to evaluate statistical significance, except in cases, as specifically noted, for which one or more expected cell frequencies was less than or equal to five, where a two tailed Fisher's exact test (FET) was used. In addition to the crude analysis described above, stepwise logistic regression analysis[21] was used to evaluate the effect of exposure risk factors, effect modifiers, and potential confounders identified in the crude analysis.

Results

Between 1982 and 1990, the PISP source file contained records for 4,177 reports associated with suspected cases of systemic illness following exposure to one or more OP compounds. A total of 4,090 records contained sufficient information to classify the relationship between exposure and illness according to the above stated criteria, including 78 records of exposure to aldicarb (Table 1). PISP files contain records for an additional
11 exposures to aldicarb that involved no symptoms of systemic illness and 4 lacking sufficient information to classify the illness-exposure relationship. In 48 (61.5%), of the cases of suspected systemic poisoning, aldicarb was the only cholinesterase inhibitor involved. In 30 (38.5%), the reported exposure involved at least one organophosphate compound, with 29 (96.7%) of this subgroup derived from a fire in 1986 at a pesticide storage facility.

Comparison to other OP compounds - selection of case and control subjects

Of the 4,090 exposures with sufficient information to classify, 1753 (42.9%) involved agricultural employment. The exposures related to agricultural employment included 408 subjects with ChE-related illness; 5 of these subjects were excluded because the OP compound involved was unknown or not specified

in the investigation. The case group therefore included 403 subjects. Of the 1,345 subjects without demonstrable ChE related illness, 764 (56.8%) met the criteria for inclusion as controls. This group included 554 subjects (72.4%) with non-specific symptoms possibly compatible with ChE illness, but ChE values in the population normal range; 31 subjects (4.1%) who had symptoms compatible with ChE-related illness, but no change from baseline ChE activities (definite evidence of lack of ChE inhibition); 10 subjects (1.3%) who had unrelated medical diagnoses; 48 subjects (6.4%) who had one or more irritant symptoms and no symptoms compatible with ChE related illness and no evidence of ChE depression; and 121 subjects with symptomatic exposure who had no evidence of ChE depression. The total number of subjects meeting the case-control criteria was thus 1,167, including 15 subjects with exposure to aldicarb and 1,152 subjects with exposures to other ChE inhibitors.

Data on illness and demographic characteristics for the cases and control subjects are shown in Appendix 1. There were several minor differences between case control subjects by demographic variables, and large differences by hospitalization, disability, and degree of ChE inhibition present. In addition to aldicarb, the exposures occurring most frequently to both cases and controls included mevinphos, methomyl, oxydemeton-methyl, parathion, phosalone, dimethoate, methamidophos, diazinon, chlorpyrifos, azinphos-methyl, methidathion, and demeton.

Among the 1,167 cases meeting case-control criteria, the overall frequency of definite and probable illness for PISP cases associated with exposure to aldicarb did not differ significantly from PISP cases associated with other cholinesterase inhibitors ($OR = 1.67$, $p = 0.471$ by Yates P^2). No significant difference in the frequency of ChE-related illness was noted when the comparison was restricted to exposures involving a single ChE inhibitor ($OR = 1.56$, $p = 0.55$). No comparison was made between the mixtures of aldicarb and mixtures containing other ChE inhibitors because there were only 3 aldicarb exposures in this category.

Exposure Categories

Table 1 displays a breakdown of exposures by illness and exposure category for the 78 exposures involving suspected systemic illness. There were 27 application associated cases including five resulting from direct exposure to aldicarb, 14 from routine application, and eight from documented violations of proper application procedure. There were six cases resulting from field reentry, two from reported exposure to aldicarb drift, 12 cases resulting from accidental ingestion of aldicarb or aldicarb-contaminated produce, and 30 miscellaneous cases. Twenty-nine of the latter cases resulted from a warehouse fire involving potential exposure to smoke laden with aldicarb, two organophosphate cholinesterase inhibitors, and their pyrolysis products. Each exposure category is discussed in more detail below.

Application associated and direct exposure cases

Of the five exposures that involved direct exposure, all identified aldicarb as the primary pesticide exposure and all were derived from either application of aldicarb or maintenance of application equipment (Table 3). Other application related cases accounted for 22 (28.9%) of the 76 cases of suspected systemic illness. Application associated cases included 13 reports linked with reported routine application of aldicarb, one case associated with mixed exposure to aldicarb and chlorpyrifos (322-86) and 8 cases involving reported violations of proper application procedure (Table 3). By crop, nursery applications accounted for nine (33.3%) and applications to cotton 12 (44.4%) of the 27 combined application and direct exposure cases. Two of the remaining cases occurred during applications to sugar beets and alfalfa, and one occurred in an employee of an agricultural pest control firm mixing/loading aldicarb for application to an unspecified crop.

Together direct and other application related exposures had a non-significantly increased frequency of ChE-related illness compared to cases in the remaining exposure categories ($OR = 2.63$, $p = 0.124$ by FET). The frequency of ChE-related illness in this category did not differ significantly from that found for application related cases associated with other cholinesterase inhibitors ($OR = 1.33$, $p = 0.7634$ by FET). A similar relative frequency of illness was observed when the comparison was restricted to cases (Table 2, block 2) involving single cholinesterase inhibitors ($OR = 1.68$, $p = 0.81$).

Drift and field residue exposure

Five residue exposures and both of the drift cases involved suspected systemic illness. Of these cases, one proved unlikely to be related to cholinesterase inhibition based upon the reported absence of any change in baseline cholinesterase values (925-89), and the remaining 6 systemic cases (including both drift cases) were judged possibly related to cholinesterase-inhibition based upon the reported exposure to residue and the presence of compatible, but not specific symptoms. Additional cases associated with exposure to field residue, included nine that involved skin rashes possibly attributable to aldicarb residue (Table 6). However, several were greenhouse workers with confounding exposures to other sources of dermatitis (ID numbers 241-82, 2140-84, 1913-82, and 1335-89) and one had a prior history of eczema (357-82).

None of the field residue exposures involved ChE-related illness. However, this frequency of ChE-related illness was based on only six cases (Table 1) and was not statistically significant from the remaining aldicarb exposure categories (OR = undefined, $p = 0.58$, by FET). Only one subject with aldicarb field residue exposure met criteria for inclusion in the case-control file and did not have ChE related illness. As expected, comparison with other ChE inhibitors produced an undefined odds ratio and showed that the reduction of frequency of illness for aldicarb associated field residue exposures was not statistically significant when compared to other ChE inhibitors.

Miscellaneous occupational exposure

A warehouse fire involving possible exposures to aldicarb, chlorpyrifos, acephate and their pyrolysis products accounted for an additional 29 cases in the miscellaneous occupational exposure category. Of these cases, 21 were asymptomatic emergency response personnel and two were nursery workers who sought precautionary medical evaluations. A worker from a nearby restaurant suffered nonspecific symptoms compatible with both cholinesterase inhibition or smoke inhalation. The remaining five cases resulting from this fire were non-occupational (discussed below).

Non-occupational exposures

A cluster of non-occupational exposures occurred in 5 individuals residing in the vicinity of the warehouse fire described above who sought medical evaluation for possible exposure to smoke laden with aldicarb, chlorpyrifos, and acephate. Three had non-specific symptoms compatible with cholinesterase inhibition, one sought treatment for symptoms compatible with upper respiratory irritation, and one was asymptomatic but sought precautionary medical evaluation (cases 1819-86, and 1823-86 to 1826-86).

Accidental ingestion accounted for 12 of the non-occupational exposures to aldicarb. The most serious ingestion case involved a near fatal childhood poisoning of a 2-year old girl who resided in a trailer at the edge of a field being planted with aldicarb treated cotton seed (630-90). Details of this case are available in a prior DPR report.[22] Eleven cases resulted from possible ingestion of aldicarb residues in illegally treated produce, but included only two cases (1460-85 and 1609-85) resulting from a large cluster estimated to involve several hundred individuals who ingested contaminated watermelon in 1985.[23] Four cases resulted from illegal application of aldicarb to squash grown in a home garden (893-83 and related cases), a single case from a similar application of aldicarb to a garden fruit tree (1583-83), and four cases involved a family that ingested parts of watermelon intended for seed production that contained 0.3 ppm of aldicarb.

Compared to cases in the remaining exposure categories, the aldicarb ingestion cases showed a significantly higher frequency of definite and probable illness (OR = 8.43, $p = 0.0036$). No comparison with ingestion cases associated with other cholinesterase inhibitors was made because the aldicarb ingestion cases did not meet the agricultural employment case-control selection criterion.

Discussion

Although the California PISP program offers a unique population based data source for evaluating the occurrence of pesticide illnesses, several limitations of the PISP data deserve consideration. For cases that are reported to the system, complete understanding of the exposure-illness relationship is hindered by lack of routine access to medical records to obtain test results where the cholinesterase test was ordered, and by the apparent failure of physicians to order cholinesterase analysis for a portion of the cases. Reporting of symptoms in medical records, PIRs, and DFRs may also be incomplete, so that the presence or absence of critical diagnostic signs may have been incompletely recorded on the available records. Understanding of the circumstances of exposure also may have been limited in some instances because of fear that disclosure of violations of legal requirements would result in enforcement penalties.

Understanding the limitations of the illness investigation process is critical in evaluating the two definite (322-86 and 1089-89), one probable (489-85), and 11 possible cases associated with the routine application of aldicarb (Table 3). Although the occurrence of ChE-related illness following routine applications implies that the safety of current practices for handling aldicarb deserve careful scrutiny, the frequency is very similar to that reported for other cholinesterase inhibitors (Table 2). Because of the potential reporting bias described above, it is possible that some of ostensibly routine applications did involve undocumented violations of proper application procedures.

The absence of definite and probable systemic field worker poisoning cases associated with aldicarb observed in this series of cases, may be due to the nearly exclusive use of this material as a pre-plant treatment and its heavy use on crops such as cotton that involve little or no hand labor. However, because the classification scheme used by PISP relies heavily on the presence of cholinesterase inhibition, it could also result from the difficulty in detecting the more transient inhibition associated with carbamate compared to organophosphate exposures. All comparisons between aldicarb and the organophosphate associated cases are limited by this difference in the toxicology of the two classes of insecticides. The comparisons were also limited to exposures related to agricultural employment, neglecting the category of non-occupational exposures to aldicarb residue on food that accounted for nearly half of the aldicarb ChE-related poisonings.

As noted in a previous case series of aldicarb associated illnesses reported by the product registrant,[24] the occupational exposures in our series of systemic poisoning cases were principally associated with application or warehouse work involving direct handling of the material. Many cases involved failure to follow recommended handling practices. Correspondingly, nearly all of the definite and probable non-occupational poisoning cases, resulted from illegal use of aldicarb on watermelons and other food crops. In 1985, there was a major crisis due to aldicarb contaminated watermelon sold in California[25] and Oregon.[26] In the Oregon portion of the outbreak there were 61 definite and 43 probable poisoning cases and in California 692 probable cases were identified. The PISP data discussed here include only two cases (1460-85, 1609-85) related to the outbreak. Although the case definition employed in the investigation of that outbreak, differed from that included here, it is probable that there were several dozen cases associated with the 10 melons documented to be contaminated with aldicarb that might have met the surveillance criteria used in this study. It is apparent that the cases associated with the outbreak were grossly under-reported to the state surveillance program. Although cases related to two additional outbreaks associated with aldicarb contaminated produce were included in our series, it cannot be estimated whether additional outbreaks may have gone undetected.

The near-fatal case of childhood poisoning included in this series (630-90) bears striking similarity to two cases reported by the aldicarb registrant in 1988 to the California Department of Food and Agriculture. In that episode, which occurred in Quitaque, Texas, a 6-year old and 3-year old boy were poisoned while playing on a trailer that contained cotton seed and an open container of aldicarb. Children who live or work in agricultural settings deserve special consideration in evaluating the risks associated with the farm environment. In addition to the well described exposures to the hazards of farm machinery,[27,28] children living on farms have many opportunities for exposure to highly toxic farm chemicals.

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Table 1 - Exposure versus Illness Category 1982-1990 Aldicarb Associated Cases n = 78

Exposure Category	Illness Category						
	1 = *Definite*	**2** = *Probable*	**3** = *Possible*	**4** = *Unlikely/ unrelated*	**5** = *Non-CHE effect*	**7** = *No symptoms*	**Row Total**
1 = *Direct eye/skin exposure*	2		3				5
2 = *Drift exposure*			2				2
5 = *Normal fieldwork*			4	1	1		6
7 = *Normal application*	2	1	11				14
8 = *Violation of proper application procedure*	2		6				8
9.0 = *Ingestion of pesticide residue*		5	6				11
9.1 = *Ingestion of pesticide concentrate/tank mix*		1					1
10 = *Other*			5		2	24	31
Total	6	7	37	1	3	24	78
Aldiicarb exposures that meet case-control selection criterion n = 15							
1 = *Direct eye/skin exposure*	2						2
5 = *Normal fieldwork*				1			1
7 = *Normal application*	2	1	3				6
8 = *Violation of proper application procedure*	2		1				3
10 = *Other*					1	2	3
Total	6	1	4	1	1	2	15

Table 2 Aldicarb vs. exposures to other ChE inhibitors n = 1,167 study subjects

Case Control Status	Definite/ Probable Cases	Other	Total	Definite/ probable cases	Other	Total	Odds Ratio	p value
Exposure Category	*Aldicarb n=15*			*1982-1990 OP cases n=1,152*			*Statistical Comparison*[b]	
All application associated categories	7	4	11	202	154	356	1.33	.7634
Direct	2	0	2	74	25	99	undefined	1.000
Normal application work	3	3	6	97	115	212	1.19	1.000
Violation of proper application procedure	2	1	3	31	14	45	0.90	1.000
Normal field reentry	0	1	1	82	108	190	undefined	1.000
Overall File	7	8	15	396	756	1152	1.67	0.471
Subtotals shown in italics for application categories (direct exposure, normal application, and violation of proper application procedure). Total for overall file includes 610 miscellaneous exposures (3 involving aldicarb and 607 involving other ChE inhibitors) for which odds ratios were not calculated.								
Aldicarb (n = 12)				*Other single ChE inhibitors (n=607)*				
All application associated categories	6	4	10	109	122	231	1.68	0.81
Direct	2	0	2	49	22	71	undefined	0.59
Normal application work	2	3	5	47	86	133	1.22	1.000
Violation of proper application procedure	2	1	3	13	14	27	2.15	1.000
Normal field reentry	0	1	1	77	89	156	undefined	1.000
Overall File	6	6	12	237	370	607	1.56	0.553
Subtotals shown in italics for application categories (direct exposure, normal application, and violation of proper application procedure). Total for overall file includes 222 miscellaneous exposures (1 involving aldicarb and 221 involving other ChE inhibitors) for which odds ratios were not calculated								

[b] Probability calculated by Fisher's two-tailed exact test

Table 3 Application Associated Exposures to Aldicarb

ID	PESTICIDES	EXPO-CLASS	CHE-NORM	RBC-DELTA	PLA-DELTA	ILL-CLASS	HOSP	DISAB	COMMENT
Direct exposures to aldicarb									
224-87	Aldicarb	1.0	5.0	U	U	5.0	0	0	Unloading boxes of Temik® when dust got in eye. Report does not state whether or not eye irritation developed. No systemic symptoms occurred.
659-87	Aldicarb	1.0	3.0	U	U	5.0	0	0	After applying Temik® he had contact with a plant leaf and got a granule of the insecticide in his eye. He shortly developed eye irritation and tearing. After his eye was rinsed and he was examined by a doctor, he was able to return to work.
412-84	Aldicarb	1.0	3.0	U	U	3.0	0	0	Without using safety equipment, worker was fixing a tractor used for applying Temik® as a pre-plant treatment to cotton. He unplugged hopper apparently while in the field, then experienced burning eyes and dizziness.
2532-84	Aldicarb	1.0	3.0	U	U	3.0	0	1	Individual removed gloves to clean Temik® gun, otherwise protective equipment had been worn. Symptoms included nausea, vomiting and dizziness.
203-82	Aldicarb	1.0	4.1	U	55.56	2.0	0	0	Got Temik® in his eye. 2 Hours later he became sick, with symptoms of headache, dizziness, nausea, sweating.
469-82	Aldicarb	1.0	4.1	36.50	93.64	2.0	4	0	Was exposed to Temik® 15g as he attempted to clean clogged nozzle and experienced marked muscular weakness, pinpoint pupils, bradycardia, and slurred speech.
528-82	Aldicarb	1.0	5.0	U	U	3.0	0	5	Had nausea and headache during two weeks of loading Temik®. He ate his lunch with hands covered with insecticide dust as there was no available water for washing.

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Table 3 Application Associated Exposures to Aldicarb

ID	PESTICIDES	EXPO-CLASS	CHE-NORM	RBC-DELTA	PLA-DELTA	ILL-CLASS	HOSP	DISAB	COMMENT
Routine application exposure									
620-90	Aldicarb	7.0	4.0	0.00	0.00	3.0	0	1	Mix/loader loading aldicarb into tractor loaded into back of cotton planter also riding on back of cotton planter to watch planting and aldicarb being applied. Symptoms: upset stomach, dizziness, and slight rash on abdomen. Diagnosis: contact dermatitis
781-89	Aldicarb	7.0	3.0	U	U	3.0	0	1	Worker reportedly was wearing all safety equipment provided while applying aldicarb, but began suffering from a cough, dizziness and headache.
1089-89	Aldicarb	7.0	4.3	61.05	3.17	1.0	0	3	Loading aldicarb granules. Wearing coveralls, rubber gloves and boots, goggles and respirator. Symptoms-headache, stomach ache, light headedness, weakness, dizziness, diarrhea, hot-cold flashes and fever. ChE plasma at low normal value, RBC -50% of low normal.
2675-89	Aldicarb	7.0	3.0	U	U	3.0	0	0	Wearing Tyvek® suit, hood, rubber boots, gloves, respirator. Worker developed itchy rash, headache, dizziness after applying pesticides. Diagnosis-cholinesterase toxicity and allergic dermatitis. Employee has left the country, information from the employer.
1444-87	Aldicarb	7.0	5.0	U	U	3.0	0	0	Worker was mixing & loading a granular chemical when some of the dust blew under his respirator. He developed a headache and stomach ache.
200-86	Aldicarb Dienochlor Fluvalinate Permethrin	7.0	3.0	U	U	5.0	0	0	Applicator developed red itchy spots on hands after working with pesticides.
322-86	Aldicarb chlorpyrifos fluvalinate	7.0	4.1	U	74.00	1.0	0	0	Applicator developed nausea, abdominal pain, and urinary urgency after applying pesticides. Plasma cholinesterase was depressed 50% below lower limit of normal range. Worker was wearing rubber boots, gloves, respirator, coveralls.
425-86	Aldicarb	7.0	5.0	U	U	6.0	0	0	Planting cotton became ill.
470-85	Aldicarb	7.0	5.0	U	U	3.0	3	5	Mixer/loader was emptying bags of Temik® and became seriously ill.
489-85	Aldicarb	7.0	4.0	0.00	0.00	2.0	0	2	While working around Temik®, developed pinpoint pupils, stomach cramps and chest pains.

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Table 3 Application Associated Exposures to Aldicarb

ID	PESTICIDES	EXPO-CLASS	CHE-NORM	RBC-DELTA	PLA-DELTA	ILL-CLASS	HOSP	DISAB	COMMENT
1011-84	Aldicarb	7.0	5.0	U	U	3.0	0	1	Persistent headache after loading Temik®
308-83	Aldicarb	7.0	3.0	U	U	3.0	0	4	Applying Temik® with spoon to hanging (potted) plants. Adequate protective gear (gloves & coveralls) worn, no unusual exposures, but developed dizziness, headache and chills. Clinical diagnosis was flu rather than aldicarb exposure.
1040-83	Aldicarb	7.0	3.0	U	U	3.0	0	0	While applying Temik® in greenhouse he became ill.
1041-83	Aldicarb	7.0	3.0	U	U	3.0	0	0	While applying Temik® in greenhouse he became ill.
1308-82	Aldicarb	7.0	1.0	0.00	0.00	3.0	0	2	During routine application of aldicarb to alfalfa, worker developed eye irritation, stuffy nose, vomiting and nausea. Cholinesterase was normal.
1689-82	Aldicarb	7.0	1.0	0.00	0.00	3.0	0	0	During routine application of aldicarb to cotton, worker developed headache, coughing, vomiting and nausea. Cholinesterase was reported to be in normal range.
Violation of proper application procedure									
1277-90	Aldicarb	8.0	3.0	U	U	3.0	0	0	Employee handling Temik® and riding on back of cotton planter felt dizzy, nauseous and upset stomach. Wearing normal work clothing, respirator, and goggles. Diagnosis-possible reaction to hazardous substance.
1561-90	Aldicarb	8.0	3.0	U	U	3.0	0	0	Worker loading pesticide into tractor loader developed rash, nausea and abdominal pains. No protective equipment provide to employee.
1215-88	Aldicarb	8.0	4.2	19.00	63.00	1.0	2	8	Worker opened up hopper box containing aldicarb to evaluate how full it was. Wind gust blew some of the material into his mouth. Began feeling stomach cramps, nausea 30 minutes later. Normally wears all protective equipment but did not have respirator at time of exposure.
1969-87	Aldicarb	8.0	5.0	U	U	3.0	0	1	While cleaning out tractor gandy boxes containing residual aldicarb dust this worker did not wear provided safety equipment. He subsequently developed headache, nausea, and vomiting.

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Table 3 Application Associated Exposures to Aldicarb

ID	PESTICIDES	EXPO-CLASS	CHE-NORM	RBC-DELTA	PLA-DELTA	ILL-CLASS	HOSP	DISAB	COMMENT
1788-86	Aldicarb	8.0	3.0	U	U	3.0	0	0	Employee applied a restricted material without proper training and became ill several hours later.
2112-86	Aldicarb	8.0	3.0	U	U	3.0	0	0	Employee was applying 1-2 oz. of Temik® 10g to 10 gal pyrus sp. He wore no respirator, gloves & had no training. He went into convulsions 4 hrs after the start of the application.
2494-84	Aldicarb	8.0	3.0	U	U	3.0	0	0	While disposing of spent containers, worker inhaled dust causing headache and eye irritation
557-83	Aldicarb	8.0	3.0	U	U	6.0	1	3	Did not wear gloves or mask during loading.
1070-83	Aldicarb	8.0	2.0	U	U	1.0	1	1	Aqua II penetrated into his respirator & when he removed it, he inhaled Temik.® Nausea & diarrhea followed.
563-82	Aldicarb	8.0	4.0	0.00	0.00	3.0	0	6	Wore respirator while applying aldicarb, but said it did not fit properly, and developed vomiting, shortness of breath, abdominal pain and diarrhea

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Table 4 Field/nursery worker exposure to aldicarb

ID	PESTICIDES	EXPO CLASS	CHE-NORM	RBC-DELTA	PLA-DELTA	HOSP	DISAB	ILL-CLASS	COMMENT
736-84	Aldicarb	5.0	5.0	U	U	0	0	5.0	Two employees of U.C. Extension came into contact with water & mud in a cotton field which had been injected with Temik® 7 days earlier.
2140-84	Glyphosate Acephate Aldicarb Weed oil	5.0	3.0	U	U	0	0	5.0	The rash has an unknown origin. Two likely possibilities: 1) The chemicals listed above; 2) A known allergic reaction to banana squash which she has had to work with on occasion.
357-82	Aldicarb	5.0	3.0	U	U	0	0	5.0	Has eczema, and a history of being allergic to various things.
241-82	Aldicarb	5.0	3.0	U	U	0	0	5.0	Was working in a greenhouse which had been treated with Temik® 2 weeks earlier. She had swelling around her eyes.
52-83	Aldicarb	5.0	5.0	U	U	0	0	3.0	Was watering plants treated with Temik® 2 days previously and developed light-headedness and tightness in the chest.
737-84	Aldicarb	5.0	5.0	U	U	0	0	3.0	Two U.C. Extension employees came into contact with water & mud in a cotton field which had been injected with Temik® 7 days earlier.
2504-85	Chlormequat HCL Aldicarb	5.0	5.0	U	U	0	0	3.0	Worker became ill after entering a greenhouse treated 1 day previously with Cycocel® (chlormequat HCL) and 6 days previously with Temik®.
849-90	Aldicarb Acephate Metalaxyl Benzylthio-cyanate	5.0	5.0	U	U	0	2	5.0	Exposed during cotton planting season. Developed rash on arms and back of neck. He loads hoppers with treated cotton seed another worker does the loading of Temik®. Saw doctor for blistering rash on arms and neck 1 month after development.
1913-82	Aldicarb	5.0	3.0	U	U	0	0	5.0	Greenhouse soil had been treated with Temik®, worker developed burning and swelling of the hands.
2692-82	Aldicarb	5.0	5.0	U	U	0	7	3.0	Worked in area treated with Temik® and then developed tightness of chest, coughing, nervousness, depression, insomnia, weakness, and epigastric distress.

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Table 4 Field/nursery worker exposure to aldicarb

ID	PESTICIDES	EXPO CLASS	CHE-NORM	RBC-DELTA	PLA-DELTA	HOSP	DISAB	ILL-CLASS	COMMENT
925-89	Aldicarb	5.0	1.1	0.00	0.00	0	0	4.0	After obtaining root samples of nursery plants previously treated with aldicarb he began experiencing headaches, muscle and stomach pains and weakness. CHE test compared to previous baseline was normal.
1335-89	Iprodione Aldicarb Benomyl Ferbam	5.0	3.0	U	U	0	0	5.0	Worker developed a rash on her lower forearms, abdomen and face after harvesting chrysanthemums and carnations. She wore rubber gloves, long sleeved shirt, pants. Exact work area where rash was caused is not known and multiple chemicals used in the nursery.
1798-88	Aldicarb B. Thuring. Chlorpyrifos	5.0	3.0	U	U	0	0	5.0	Weeding in cotton field treated with aldicarb more than 1 month earlier, and Lorsban® and Javelin® 2 months previously, broke out in rash on body and extremities. Has a history of childhood rashes.
847-88	Aldicarb	5.0	3.0	U	U	0	0	5.0	Mulching cotton for replanting in a field treated with aldicarb 24 days earlier at first planting; broke out with rash on neck; spread to face, shoulders, upper arms and chest. Employee was in an enclosed cab, but said he could smell the aldicarb

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Table 5 Miscellaneous occupational exposure cases

ID	PESTICIDES	EXPO CLASS	CHE-NORM	RBC-DELTA	PLA-DELTA	HOSP	DISAB	ILL-CLASS	COMMENT
59-82	Aldicarb	2.0	3.0	U	U	0	0	3.0	Was walking past greenhouse being treated with aldicarb and developed headache and dizziness.
488-85	Aldicarb	2.0	5.0	U	U	1	2	3.0	Was repairing a flat near vicinity of Temik® bags being burned, and developed dizziness, nausea, weakness and chest tightness.
743-84	Aldicarb	10.0	3.0	U	U	0	1	3.0	Inhaled dust of Temik® concentrate in a warehouse, developed headache and odd feeling of disorientation.
981-82	Aldicarb	10.0	1.0	0.00	0.00	0	3	5.0	Employee was burning Temik® bags. Possible smoke inhalation.

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Table 6 Non-occupational Exposure to Aldicarb

ID	PESTICIDES	EXPO-CLASS	CHE-NORM	RBC-DELTA	PLA-DELTA	ILL-CLASS	HOSP	DISAB	COMMENT
630-90	Aldicarb	9.1	4.4	U	U	1.0	2	0	Child playing in field; symptoms-muscle fasciculations, diarrhea, pinpoint pupils, stomach cramps, difficulty breathing, edema. Child may have eaten granules. Gandy boxes on tractor full of Temik® near mobile home where child lived and ground around the home was contaminated with aldicarb granules.
1503-87	Aldicarb	9.0	3.0	U	U	3.0	0	0	A family had nausea, stomach cramp, sweating and diarrhea from eating watermelon grown for seed production. The CDFA lab in Fresno found 0.3 ppm aldicarb sulfoxide in the melon but none in soil sample or other melons taken from the plot.
1819-86	Chlor-pyrifos Acephate Aldicarb	10.0	3.0	U	U	3.0	0	U*	Person was in area of fire and inhaled smoke. Complained of being lightheaded.
1823-86	Chlor-pyrifos Acephate Aldicarb	10.0	3.0	U	U	3.0	0	0	Person in area of fire. Complained of shortness of breath, light headedness. Has history of asthma.
1824-86	Chlor-pyrifos Acephate Aldicarb	10.0	3.0	U	U	3.0	0	0	Lives in area of fire; complained of nausea, dizziness and headache.
1825-86	Chlor-pyrifos Acephate Aldicarb	10.0	3.0	U	U	3.0	0	0	Lives in area of fire. Complained of tingling of lips. Not available for interview.
1826-86	Chlor-pyrifos Acephate Aldicarb	10.0	3.0	U	U	3.0	0	0	Lives in area of fire. Complained of visual problems, diarrhea and weakness.
1460-85	Aldicarb	9.0	3.0	U	U	2.0	0	0	After eating watermelon she developed vomiting, diarrhea, dizziness, sweating and pain in lower abdomen.
1609-85	Aldicarb	9.0	3.0	U	U	3.0	0	0	Women became ill after eating watermelon.

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Table 6 Non-occupational Exposure to Aldicarb

ID	PESTICIDES	EXPO-CLASS	CHE-NORM	RBC-DELTA	PLA-DELTA	ILL-CLASS	HOSP	DISAB	COMMENT
893-83	Aldicarb	9.0	3.0	U	U	2.0	2	0	After eating home garden squash treated with Temik® 15g two weeks earlier, developed nausea, diarrhea, sweating, vomiting and abdominal pain. Hospitalized for two days. Urine collected in hospital showed 0.34 ppm aldicarb in analysis by product registrant.
2779-83	Aldicarb	9.0	3.0	U	U	2.0	2	0	After eating squash treated with Temik® 15g, developed sweating, abdominal cramps and weakness. See 893-83
2780-83	Aldicarb	9.0	3.0	U	U	2.0	2	0	After eating squash treated with Temik® 15g, developed nausea, vomiting and dizziness. See 893-83
2781-83	Aldicarb	9.0	3.0	U	U	2.0	2	0	Within 30 minutes after eating squash treated with Temik® 15g developed nausea, vomiting, sweating, carpal spasms, and perioral numbness. See 893-83
1583-83	Aldicarb	9.0	5.0	U	U	2.0	0	0	Ate fruit from home grown tree which had been treated with Temik® and developed nausea, dizziness, sweating, salivation, and vomiting.

ID - case number and year reported to the California Pesticide Illness Surveillance Program (PISP); **PESTPRI** - primary pesticide associated with illness; **CHENORM** - cholinesterase code **1**=reported normal in the medical record or county pesticide episode investigation report; specific values not recorded; **1.1**= test results reported normal comparable to baseline; **2**=reported depressed; specific values not recorded; **3**=no test ordered or unspecified; **4.0**=test results available, results indicate both RBC and plasma cholinesterase are greater than the lower limits of the normal range for the lab running the assay; **4.1**=test results available, results indicate either or both RBC and plasma cholinesterase are less than the lower limits of normal range for the lab running the assay; **4.2**=test results available for date of illness and also a comparison baseline test; % depression calculated for both RBC and plasma cholinesterase versus midpoint of baseline; **4.3**=test results available for date of illness and also a comparison followup test; % depression calculated for both RBC and plasma cholinesterase versus followup tests; **4.4**=lower limit of normal specified only; % depression calculated versus lower limit. **5**=cholinesterase test ordered/ results not available. **RBCDELTA** - % decrease in RBC cholinesterase; **PLADELTA** - % decrease in plasma cholinesterase; **EXPOCLASS** - exposure class: **1**=direct exposure; **2**=drift; **5**=normal fieldwork; **7**=normal application work; **8**=failure to use close system/other application violation; **9.0**=ingestion of pesticide residue; **9.1**=ingestion of pesticide concentrate; **10**=other exposures; **ILLCLASS** - illness classification; **1**=definite; **2**=probable; **3**=possible; **4.0**=unlikely/unrelated; **5**=non-CHE effect; **6**: insufficient information to classify; **8**: delayed onset neuropathy; **HOSP** - days hospitalized; **DISAB** - days disability; **U** - Unknown

Appendix 1

Comparison of case and control subjects by illness characteristics

The case and control subjects showed several minor, but statistically significant differences in demographic composition. The mean age for cases was 29.4 years of age and 31.6 for controls subjects. Males represented 87.8% of cases and only 76.6% of the control subjects. Hispanic surnames, by contrast, were more common among controls (86.5%) than among cases (73.0%). Control subjects were more likely than cases to work in crop production (69.5% of controls vs. 46.2% of cases) and cases were correspondingly more likely to work in agricultural services. For individual SIC codes, cases were less likely than average to occur among vegetable and melon workers (0161), and more likely to occur among crop protection services workers (0721). Cluster episodes accounted for 174 (43.2%) of the 403 case subjects and for 515 (67.3%) of the 765 controls.

As indicated in the definition of ChE related illness, all of the cases had one or more symptoms compatible with ChE illness; however, compatible non-specific symptoms were also present in 580 (75.8%) of the control subjects. Of the 309 subjects with definite illness, 85 (27.0%) had one or more specific symptoms of ChE depression. The probable cases by definition all had specific symptoms. Three (0.4%) of the control subjects had one or more specific symptoms, but showed no depression relative to baseline ChE measurements. Irritant symptoms were present in 114 (28.3%) of the cases and in 277 (34.5%) of the controls. Odor was noted to be present by 80 (19.9%) of the case subjects and by 371 (48.5%) of the controls.

Of the case group, 226 (56.1%) had reported ChE (either RBC or plasma) levels below the population range of normal (**Chenorm = 4.1**: median RBC depression estimated from the midpoint of the normal range = 44.9%, range 0-97.5%; median estimated plasma ChE depression was 59.3%, range 0-97.4%). Forty-three (10.7%) had both a baseline ChE test and followup at the time of illness (**Chenorm = 4.2**: median depression from RBC baseline = 48.6%, range 0-87.3%; median depression from plasma baseline = 61.7%, range 0-97.9%). Nine (2.3%) of the cases had followup tests (**Chenorm = 4.3**: median RBC depression = 23.0%, range 0-61.1%; median plasma depression = 17.3%, range 0-89.3%). For 11 cases (2.9%) only plasma ChE was reported and only the lower limit of the population range was listed on the laboratory reports (**Chenorm = 4.4**: median depression below the lower limit of normal = 45.2%; range 0-81.2%).

In the control group, 466 subjects (60.4%) had ChE levels in the population normal range (**Chenorm = 4.0**: median RBC depression below midpoint of normal range = 2.0% range 0-47%; median plasma ChE depression = 1.3%, range 0-75.0%). Nineteen (2.5%) of the control subjects had baseline tests (**Chenorm = 4.2**: median RBC ChE depression = 2.0%, range 0-19.0%; median plasma depression = 1.3%, range = 0-13.9%). Six (0.8%) of the control subjects had plasma ChE activity tested by a laboratory listing only the lower limit of normal on its reports (**Chenorm = 4.4**); all had levels above the reference point.

The large differences in ChE activity between the case and control subjects were reflected in the information on hospitalization and disability. One hundred seven (27.2%) of the 391 case subjects with information on hospitalization status spent one or more days in the hospital (median hospital stay = 2 days, range 1 - 48 days) compared to 16 (2.2%) of the 731 subjects with hospitalization information in the control group (median hospital stay = 1.5 days, range 1-6 days). Of the 315 case subjects with disability information, 219 (68.9%) had one or more days of disability (median = 5 days, range 1-71 days). Of 634 control subjects with disability information, 272 (42.9%) had one or more days of lost work time (median = 1 day, range 1 - 28 days).

The individual compounds most frequently associated with exposure to both case and control subjects was mevinphos (158 case [39.2%] and 337 controls [44.1%]). Other compounds accounting for 10 or more case subjects [with % of totals subjects and % of total control subjects as indicated] included methomyl (88 cases [21.8%] and 123 controls [16.1%]), oxydemeton-methyl (71 cases [17.6%] and 242 controls

[31.6%]), parathion (55 cases [13.6%] and 93 controls [12.2%]), phosalone (51 cases [12.7%] and 11 controls [1.4%]), dimethoate (39 cases [9.7%] and 178 controls [23.3%]), methamidophos (37 cases [9.2%] and 186 controls [24.3%]), diazinon (35 cases [8.7%] and 31 controls [4.1%]), chlorpyrifos (25 cases [6.2%] and 52 controls [6.8%]), azinphos-methyl (14 case subjects [3.5%] and 34 controls [4.4%]), methidathion (12 cases [3.0%] and 28 controls [3.7%]), and demeton (10 cases [2.5%] and 5 controls [0.7%]).